Intensive Care Med (2001) 27: 898–904
DOI 10.1007/s001340100939

EXPERIMENTAL

M. Vassiliou
C. Saunier
C. Duvivier
P. Behrakis
R. Peslin

Volume dependence of respiratory system resistance during artificial ventilation in rabbits

Received: 9 June 2000
Final revision revised: 12 February 2001
Accepted: 12 February 2001
Published online: 12 April 2001

C. Saunier · C. Duvivier · R. Peslin
Unité 14 de Physiopathologie Respiratoire,
Institut National de la Santé et de la Recherche Médicale,
Université H. Poincaré Nancy I,
54500 Vandoeuvre-les-Nancy, France

M. Vassiliou (✉)
Distomou Str. 14121, N. Herakleio, Athens, Greece
E-mail: mvassil@cc.uoa.gr
Phone: +30-1-2826231
Fax: +30-1-2826231

M. Vassiliou · P. Behrakis
Laboratory of Experimental Physiology,
Medical School, University of Athens,
Athens, Greece

Abstract The volume dependence of respiratory resistance (Rrs), usually observed during normal breathing, is expected to be accentuated during expiratory flow limitation (EFL). In order to quantify this dependence we studied the pressure, flow, and volume data obtained from eight New Zealand rabbits, artificially ventilated at different levels of applied expiratory pressure (0–10 hPa), before and during histamine i.v. infusion. EFL was provoked by lowering the expiratory pressure and was detected by the application of an additional negative expiratory pressure and by forced oscillations. The analysis of respiratory system mechanics was performed by multiple regression, using the classical linear first-order model and also a nonlinear model, accounting for volume dependence of Rrs. Both models satisfactorily fitted the data in the absence of EFL. The nonlinear model proved to be more appropriate in the presence of EFL. The coefficient expressing the volume dependence of Rrs (Rvd) was significantly more negative during EFL. Rvd values were highly correlated with the fraction of the tidal volume left to be expired at the onset of EFL. A threshold Rvd value of –1,000 ($hPa \cdot s \cdot l^{-2}$) detected EFL with high sensitivity and specificity. We conclude that a strongly negative volume dependence of Rrs is a reliable and noninvasive index of EFL during artificial ventilation.

Keywords Expiratory flow limitation · Linear regression · Volume dependence of resistance · Respiratory impedance · Respiratory elastance · Respiratory resistance · Mechanical ventilation

Introduction

Linear modeling of the respiratory system (RS), according to the regression equation: Pao = Pe+Ers.V+Rrs.V' (1) has proved a useful tool for the evaluation of respiratory mechanics during spontaneous breathing and experimental or clinical artificial ventilation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Pao, V, and V' are the airway opening pressure, the flow, and the volume, respectively. Ers and Rrs are the respiratory system (RS) elastance and resistance and Pe represents the end-expiratory pressure. Nevertheless, non-linearities are frequently present during normal breathing in healthy subjects and much more in various respiratory disorders. Flow dependence of resistance as well as volume dependence of elastance are usual in obstructive and restrictive disorders [12, 13, 14, 15, 16, 17, 18, 19].

Expiratory flow limitation (EFL), which is not uncommon under mechanical ventilation is the most typical disorder, where linear modeling of the RS is characterized by a relatively high error, leading to more or less inaccurate estimation of the mechanical coefficients [5, 6, 7, 11], since a substantial pressure drop is not accompanied by a corresponding increase of flow. This would be expressed as a progressive and severe increase of resistance throughout expiration, which actually

means that under EFL, resistance increases disproportionately as tidal volume decreases. A simple non-linear model accounting for V dependence of RS resistance is the following: Pao = Pe+Ers.V+(Rs+Rvd.V).V' (2), which differs from the linear one only by the term Rvd.V. Rs corresponds to the linear coefficient of resistance and Rvd to the V dependence of resistance coefficient. This model has been previously studied during mechanical ventilation [5, 6]. Nevertheless, as far as we know, it has not been comparatively examined under EFL and non-EFL conditions, on the basis of Rvd values.

In order to experimentally investigate this concept, models (1) and (2) were used in the analysis of Pao, V', and V data obtained from eight mechanically ventilated New Zealand rabbits with and without EFL. A better fitness of model (2) to data and, more specifically, characteristic values of Rvd, might offer a diagnostic tool for continuous EFL detection during artificial ventilation, without any intervention on the regulation of ventilation and the respiratory circuits, and with no additional demands in instrumentation infrastructure.

Methods and materials

Eight New Zealand rabbits with body weight of 2.1–2.5 kg were mechanically ventilated with the aid of a computer-controlled ventilator, built in the laboratory [21]. The respiratory frequency was set at 50 breaths/min and the tidal volume (VT) at 25 ml. The animals were anaesthetized with sodium thiopental (15–20 mg/kg, i.v.) and tracheotomized.

After connection to the ventilator, they were paralyzed with vecuronium bromide (0.8 mg, followed by continuous i.v. infusion of 0.4 mg/h). Measurements started 5 min later.

V' was measured with a Fleisch 00 pneumotachograph connected to a differential pressure transducer (Honeywell 176/14). Pao was measured by a similar transducer matched to the first one for

Table 1 End-expiratory pressure *(EEP)*, Δ*(Im)*, Rvd, and VEFL values for the eight New Zealand rabbits included in the study, before and during histamine infusion

Rabbit	EEP	Before histamine infusion			After histamine infusion		
		V EFL	Rvd	Δ(IM)	V EFL	Rvd	Δ(IM)
	(hPa)	(% VT)	(hPa·s·l^{-2})	%	(% VT)	(hPa·s·l^{-2})	%
1	0	0	–272.75	–18	0	–431.7	–3
	–5	16	–1,348.70	–128	34	–2,351.2	–111
	–8	20	–1,888.94	–71	44	–4,661.9	–381
	–10	19	–1,982.12	–73.5	40	–4,294.6	–292
2	0	0	–174.07	–22.3	0	–721.6	–5
	–5	0	–892.30	–39.4	44	–2,183.5	–155
	–8	18	–2,479.72	–67.3	19	–1,812.6	–200
	–10	20	–2,767.6	–190	25	–2,183.6	–364
3	0	0	–347.4	–24.3	0	–923.2	–12
	–5	11	–1,782.8	–60	52	–4,333.5	–166
	–8	23	–2,378.9	–110	47	–4,267.7	–270
	–10	23	–3,308.7	–396	45	–5,047.1	–435
4	0	0	–365.1	–17	0	–412.8	–13
	–5	20	–2,064.8	–74	55	–4,258.3	–245
	–8	31	–3,600.4	–264	49	–3,775.2	–363
	–10	29	–4,535.8	–388	37	–4,441.9	–476
5	0	0	–242.8	–4	0	–872.6	–15
	–5	10	–1,202.8	–22.4	67	–5,615.3	–291
	–8	17	–2,529.9	–95	67	–5,974.8	–548
	–10	21	–3,740.5	–227	49	–6,515.7	–722
6	0	0	–387.6	–22	0	–815.2	–13
	–5	0	–945.8	–7	48	–4,536.8	–276
	–8	12	–1,946.3	–72	41	–4,720.3	–365
	–10	17	–2,727.8	–74	41	–5,614.7	–512
7	0	0	–219.6	–14	0	–915.9	–15
	–5	10	–1,330.8	–13	62	–5,282.6	–212
	–8	22	–2,652.1	–112	51	–5,751.8	–446
	–10	25	–3,708.1	–196	46	–6,095.4	–524
8	0	0	–359.7	–23	0	–475.6	–18
	–5	0	–899.6	–24	42	–3,390.8	–229
	–8	10	–1,592.3	–77	28	–2,688.2	–231
	–10	17	–2,718.66	–156	22	–2,282.7	–110

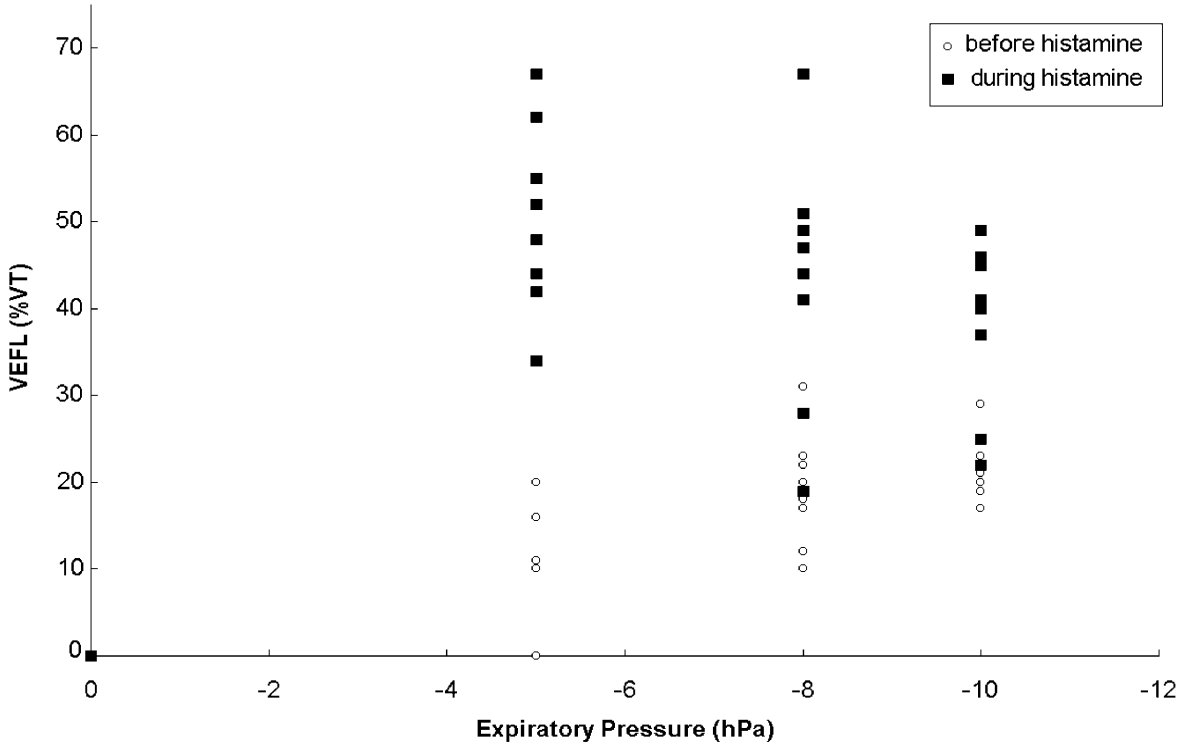

Fig. 1 Scatter diagram showing the relationship between the fraction of the tidal volume left to be expired at the onset of EFL (VEFL) and the applied expiratory pressure, before and during histamine infusion in eight New Zealand rabbits

amplitude and phase (± 2 % and ± 2 °, respectively) up to 15 Hz. The flow- (V') measuring device was calibrated with a 30 ml syringe (integral method) and Pao with a slanted fluid manometer. A constant inspiratory flow and a constant EEP were set during the measurements. The level of the EEP (0–10 hPa) could be modified at will from the computer without interruption of ventilation. During the forced oscillation (FO) measurements, a 15 Hz sinusoidal signal was applied to a 30 W horn driver-type loudspeaker (Boyer, 2R409) connected to the inspiratory line of the respirator, resulting in pressure oscillations at the airway opening of 1–3 hPa peak to peak.

The same type of endotracheal tube (ET) was used in all experiments (55 mm length and 3.8 mm internal diameter) and its pressure-flow relationship was determined in vitro (ET resistance = 7.41 $hPa \cdot s \cdot l^{-1}$).

Measurements were made at EEPs of 0, –5, –8, and –10 hPa, in a random sequence, while full inflation with EEP of 5 hPa was applied before each measurement in order to prevent atelectasis. Pao and V' were digitized at a rate of 180 Hz with a 12-bit analog-to-digital/digital-to-analog conversion board (PCLab, Digimétrie, Perpignan, France). They were stored for periods of 7.2 s (six respiratory cycles) for later analysis. At each level of EEP, a first recording was made during which, in order to test if EFL was present [20], a further negative pressure of 5 hPa was applied during expiration (NEP) for one of the six recorded cycles. Then, two or three consecutive recordings were made both with and without the added FO. The same sequence of measurements was repeated 5 min after administration of histamine into the left jugular vein (initial dose of 800 μg/kg followed by continuous infusion at 4000 μg/kg per hour).

The recorded data were treated offline with specifically developed software. V was calculated by numerical integration of V' and the pressure signal was corrected for the pressure drop along the ET. The presence of EFL at a given level of EEP was determined by comparing the flow-volume relationship of the NEP cycle to that of the preceding cycle. When EFL was present (V' unchanged by lowering EEP) the fraction of the VT left to be expired at the onset of EFL (VEFL) was measured. Signals without FO were analyzed by multiple linear regression on a cycle per cycle basis according to models:

$$Pao = Ers.V + Rrs.V' + Pe \quad (1)$$

$$Pao = Ers.V + (Rs + Rvd.V).V' + Pe \quad (2)$$

where Pe corresponds to the Pao value, when V and V' are nil (end expiration). In the second model Rs is the value of Rrs at end expiration (V = 0) and Rvd expresses the change in Rrs per volume unit.

All coefficient values were averaged for the six consecutive cycles included in the recording, since their inter-cycle coefficient of variation was less than 3 %. The root mean square difference ($RMSD = (\sum(Pao_{pred}-Pao_{meas})^2/n)^{1/2}$) between the actually measured and the calculated pressure according to the right member of equations characterizes the fit of the model to the data.

In the recordings with FO, the Fourier coefficients of Pao and V' at 15 Hz were computed for each oscillation cycle separately (18 for each respiratory cycle) and used to obtain the real (Re) and the imaginary (Im) parts of the RS impedance (Zrs). Re and Im values of the inspiratory and expiratory breathing phases were separately averaged. The phasic variations of Im, a reliable index of EFL [21], were characterized by relating the difference between expiratory and inspiratory mean values to the inspiratory imped-

ance modulus: Δ(Im) = 100.(Im,exp – Im, insp)/|Zrs,insp|) at each level of the applied EEP [21].

Mean values of Rvd, VEFL (% VT), and Δ(Im) obtained from recordings with the same EEP in each rabbit were averaged before and during histamine administration separately (Table 1).

Besides the multiple regression analysis, a paired *t*-test was used to evaluate the significance of the differences between the calculated values of Ers and Pe according to both models. RMSDs of the two models were compared with the aid of the *F*-test. The fits observed with the two models can also be comparatively evaluated using the criteria set by Rousselot et al. [6]; reduction of RMSD by at least 20 % and at least 0.3 hPa.

Comparisons were made for the data as a whole as well as for the data with and without EFL, separately. Simple linear regression was used to estimate the correlation between Rvd and VEFL, Rvd and Δ(Im), Δ(im) and VEFL, at all levels of applied EEP, before and during histamine infusion.

Results

The values of Rvd, VEFL, and Δ(Im) at each level of EEP before and during histamine-induced bronchospasm in the eight rabbits are presented in Table 1, and the relationship between VEFL and EEP is shown in Figure 1.

EFL, as detected by the NEP method, was not present at 0 hPa of EEP either before or during histamine administration (VEFL = 0). EFL did not occur at EEP = –5 hPa before histamine infusion in three out of eight rabbits, but occurred in all rabbits at –8 and –10 hPa of EEP before histamine administration and at –5, –8, and –10 hPa of EEP after histamine infusion. At all levels of EEP, VEFL varied largely among rabbits, particularly after histamine infusion. It tended to increase with decreasing EEP before histamine ($r = 0.85$) but not after histamine (Fig. 1). The presence or absence of EFL, as assessed by the NEP method, was nearly always confirmed by the forced oscillation data; in all instances without EFL, Δ(Im) was above the threshold value of –50 %, and in all but two instances with EFL it was below that threshold.

Values of Ers, Rrs, Rvd, and RMSD are expressed as mean ± standard deviation. The nonlinear model fitted the data better than the linear one (RMSD: 1.47 ± 0.61 hPa compared to 1.79 ± 0.85 hPa, $P < 0.001$). The difference was small (1.26 ± 0.61 hPa vs 1.28 ± 0.61 hPa, $P < 0.001$) in the absence of EFL (Fig. 2), but quite substantial when EFL was present (1.69 ± 0.54 hPa vs 2.30 ± 0.74 hPa, $P < 0.001$). Ers was generally higher after histamine infusion than before. It was minimally lower with the nonlinear model than with the linear one (765.7 ± 210.0 vs 768.9 ± 209.0 hPa.l^{-1}, respectively, $P < 0.005$) but the difference was not significant when EFL was present. Values of constant Pe were similar with the two models (–3.84 ± 4.69 vs –3.76 ± 4.77 hPa, $P = 0.2$) and did not differ significantly from the actually applied EEP, whether EFL was present or not. Rvd was generally higher before than after histamine infusion (–1794 ± 1226 vs –3364 ± 1978, $P < 0.001$). Rvd was highly correlated to VEFL at all levels of EEP. This was true for the whole data ($r = 0.92$), the data before ($r = 0.93$) and the data after histamine infusion (0.91). The overall relationship of VEFL and Rvd is shown in Fig. 3. A high correlation was also observed between Rvd and Δ(Im) ($r = 0.90$), whereas the correlation between VEFL and Δ(Im) was less narrow ($r = 0.63$). Finally, taking the NEP method as a reference, an Rvd value lower than –1000 hPa·s·l^{-2} detected EFL with a 100 % sensitivity and 100 % specificity (Table 1).

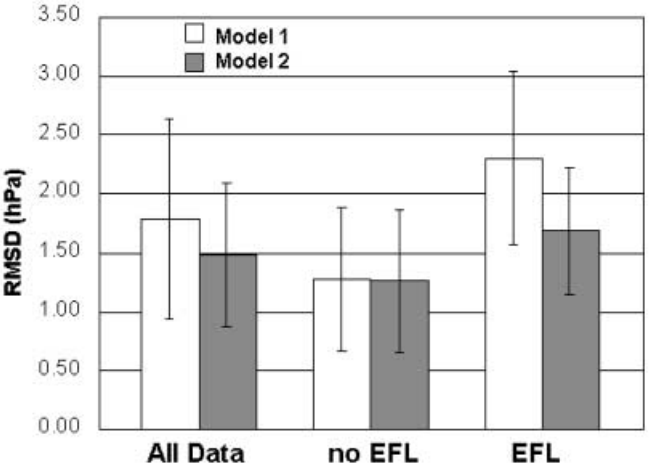

Fig. 2 Graphical presentation of root mean square difference (RMSD) as mean values ± standard deviations according to model 1 (Pao = Ers.V+Rrs.V'+Pe) and model 2 [Pao = Ers.V + (Rs + Rvd.V).V' + Pe] for all measurements *(left)*, for measurements without EFL *(center)* and for measurements with EFL *(right)*

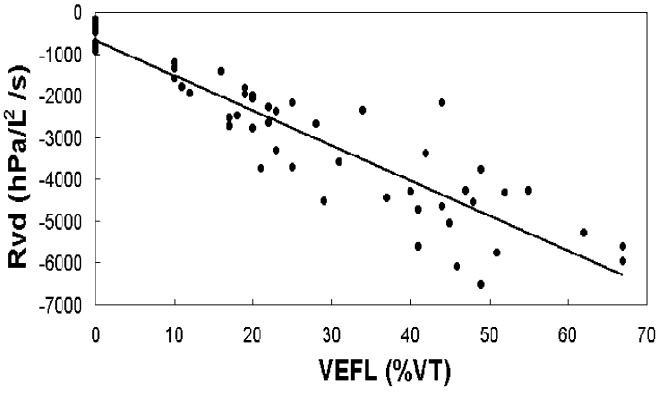

Fig. 3 Scatter diagram showing the relation between the volume dependence of resistance coefficient (Rvd, Eq. 2) and VEFL in the eight rabbits at all expiratory pressures (Rvd = –690.9 –83.685×VEFL, $r = 0.92$)

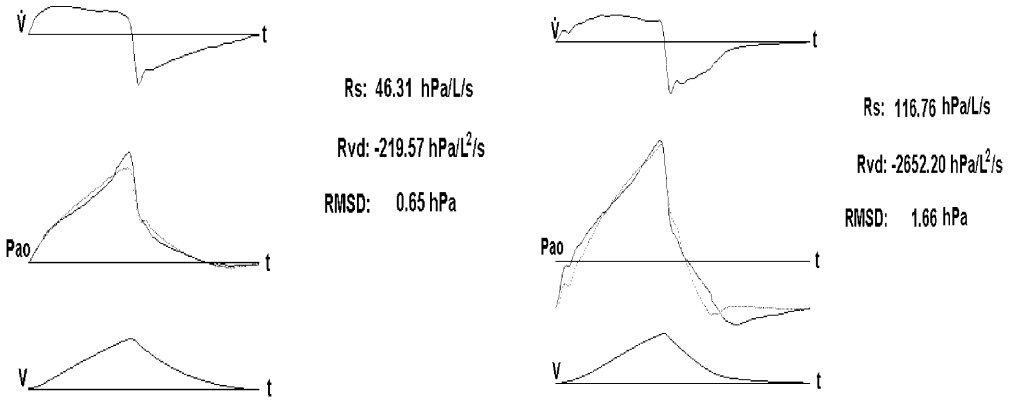

Fig. 4 Flow *(V')*, Volume *(V)* and airways opening pressure *(Pao)* recordings versus time *(t)* throughout a complete respiratory cycle **a** without expiratory flow limitation (EFL) and **b** with EFL. *Superimposed dotted line* corresponds to Pao predicted by our nonlinear model. Notice that superimposition is perfect in **a** (low RMSD), whereas a remarkable dissociation between predicted and recorded Pao *(t)* appears in **b** (high RMSD). Case **b** is also characterized by a very high and negative value of the volume dependence of resistance coefficient (Rvd)

Discussion

Linear modeling has proved useful to explore respiratory mechanics non-invasively during mechanical ventilation. Provided the subject is passive, the method is applicable during any mode of ventilation; it requires only modest space for instrumentation and does not interfere with ventilation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Despite the general appropriateness of the linear model, there are situations where the model fits the data poorly suggesting that the RS mechanical behavior deviates markedly from linearity. Such a situation is the occurrence of EFL [5]. EFL during mechanical ventilation is accompanied by ventilatory and circulatory disturbances such as dynamic lung hyperinflation, increased work of breathing, and enhanced non-uniformity of ventilation [22, 23, 24]. Therefore, the recognition of EFL is crucially important for rapid therapeutic intervention such as the application of a PEEP [25, 26] or the administration of bronchodilators [25]. A moderate negative volume dependence of Rrs is expected even in normal subjects according to the inverse relationship between airway resistance and lung volume [19]. Under EFL conditions, expiration is accompanied by a progressive airway collapse [27, 28, 31] responsible for a much higher increase in resistance with decreasing volume than in the absence of EFL. Any further increase of the expiratory driving pressure results in a larger degree of airway compression on an extended part of the airways, leading to a higher resistance with a stronger dependence upon lung volume.

In the present study, the volume dependence of Rrs was explored in situations where EFL could be induced at will by lowering the end-expiratory pressure. The presence of EFL was detected with a high degree of coincidence by two independent methods [20, 21]. The analysis of the pressure-flow-volume relationship with a model allowing for a volume dependence of Rrs fitted the data much better than the classical linear model in the presence of EFL. The index of volume dependence (Rvd coefficient) was highly correlated to the indices of EFL obtained with the NEP and the FO methods. More importantly, with a suitable threshold, it provided exactly the same information concerning EFL as the NEP method without having to disturb the mechanical ventilation in any way.

The same nonlinear model has been previously used in adults with acute respiratory failure and in neonates with various respiratory disorders during mechanical ventilation [5, 6]. Although a positive volume dependence of Rrs has been observed in some of the adult patients, a negative volume dependence was always seen in neonates. While the negative volume dependence of resistance is directly related to the airways' static and dynamic behavior, the other components of total Rrs, e.g., lung tissue and/or chest wall resistance, time constant inequalities, or high levels of applied PEEP, might explain a positive volume dependence of Rrs [13, 14, 15, 32]. In our study, a negative volume dependence of Rrs was always present but it was much more pronounced during EFL.

A substantial volume dependence of Rrs was also previously observed in rabbits during histamine-induced bronchoconstriction and shown to be responsible for serious errors in impedance measurements due to crosstalk between frequency components [31]. However, the model that best explained the results of this study was not used in the present work. This model included an expiratory resistance which varied with the reciprocal of lung volume ($Re = Ri+Kr/(V+Vo)$), where Re and Ri are the expiratory and inspiratory resistances, Kr the volume dependence term, and Vo a volume offset. Another previous study analyzed transpulmonary pressure (Ptp) and V' during spontaneous breathing from asthmatics, emphysema patients, and normal sub-

Table 2 Model analysis of recordings in a patient with normal respiratory function (1) and in a COPD patient (2) during mechanical ventilation at 0 and 5 hPa of EEP. Models 1 and 2 correspond to Eqs. 1 and 2. Data are not corrected for endotracheal tube resistance

Patient	PEEP	Model 1				Model 2				
		Ers	Rrs	Pe	RMSD	Ers	Rs	Rvd	Pe	RMSD
	(hPa)	(hPa.l^{-1})	(hPa·s·l^{-1})	(hPa)	(hPa)	(hPa·s·l^{-1})	(hPa·s·l^{-1})	(hPa·s·l^{-2})	(hPa)	(hPa)
1	0	20.01	7.12	0.67	0.69	20.02	7.25	–0.40	0.67	0.69
	5	19.51	7.10	5.78	0.63	19.52	7.14	–0.13	5.79	0.63
2	0	26.4	11.7	0.63	1.47	26.5	18.5	–24.3	0.98	1.03
	5	23.3	9.8	5.33	0.77	23.3	11.7	–6.8	5.48	0.71

jects before and after metacholine-induced bronchoconstriction [33]. A regression model containing separate inspiratory and expiratory pulmonary resistances, but also an expiratory volume dependence of resistance term, was able to detect EFL by substantially more negative values of the coefficient of this term.

Histamine-induced bronchoconstriction promotes the occurrence of EFL and its onset earlier in the expiratory phase [28, 29, 30]. This is supported by the significantly higher values of VEFL observed after histamine administration in this study. The corresponding Rvd values paralleled very closely the differences between pre- and post-histamine values of VEFL.

Although the nonlinear model significantly better fitted our EFL data than the linear one, RMSDs exceeded 1 hPa in most instances during EFL, as is shown in Fig. 4. It is most likely that other nonlinearities are also present in that situation, such as volume dependence of elastance and/or flow dependence of resistance [12, 18]. Nevertheless, the relationship observed in this study between Rvd and VEFL supports the clinical usefulness of our simple nonlinear model: it should be emphasized that a threshold value of –1000 hPa·s·l^{-2} permitted us to assess with 100 % accuracy the presence or absence of EFL, as identified by the NEP method. The high correlation between Rvd and VEFL shows that Rvd may also provide a valuable quantitative information about the severity of EFL. As a first step to assessing whether the method had a good potential in a clinical setting, we performed the same model analysis on recordings made in two mechanically ventilated patients with and without a PEEP of 5 hPa (Table 2). The first patient was a 21-year-old adult hospitalized after a car accident without any sign of respiratory disorder, whereas the second was a 65-year-old patient, a heavy smoker with known exacerbations of COPD and very likely to be flow-limited. Both models fitted almost equally well the data of patient 1 at 0 and 5 hPa of PEEP and the nonlinear model revealed a small negative volume dependence of Rrs. In contrast, the nonlinear model substantially better fitted the data obtained without PEEP in patient 2, showing the presence of a strong volume dependence of Rrs; applying a PEEP of 5 hPa almost suppressed the difference between the two models and considerably decreased Rvd. Although we have no independent evidence concerning the presence of EFL in these patients, the data are consistent with those seen in our rabbits and suggest that patient 2 was flow-limited without PEEP.

In conclusion, the analysis of the pressure-flow-volume relationship of the RS with a model allowing for volume dependence of Rrs is a promising diagnostic tool for the detection of EFL during artificial ventilation. In our experimental conditions, it provided an index of EFL in perfect agreement with the NEP method and its specificity was higher than that of the FO technique. The major advantage over the NEP method is that it does not interfere at all with the mechanical ventilation. In addition, the method is suitable for continuous monitoring in contrast with the NEP method, which is necessarily discontinuous. Further data are necessary to evaluate the sensitivity and specificity of this approach in a clinical setting and to adapt the Rvd threshold value to human respiratory mechanics.

References

1. Farré R, Peslin R, Rotger M, Navajas D (1986) Human lung impedance from spontaneous breathing frequencies to 32 Hz. J Appl Physiol 61: 81–86
2. Benhamou D, Lorino AM, Lorino H, Zerah F, Harf A (1987) Automated measurement of respiratory mechanics in anaesthetized ventilated patients. Bull Eur Physiopathol Respir 23: 423–428
3. Nicolai T, Lanteri C, Freezer N, Sly PD (1991) Non-invasive determination of alveolar pressure during mechanical ventilation. Eur Respir J 4: 1275–1283

4. Seear M, Wensley D, Werner H (1991) Comparison of three methods for measuring respiratory mechanics in ventilated children. Pediatr Pulmonol 10: 291–5
5. Peslin R, Felicio da Silva J, Chabot F, Duvivier C (1992) Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients. Eur Respir J 5: 871–878
6. Rousselot JM, Peslin R, Duvivier C (1992) Evaluation of the multiple linear regression method to monitor respiratory mechanics in ventilated neonates and young children. Pediatr Pulmonol 13: 161–168
7. Lorino AM, Harf A (1993) Techniques for measuring respiratory mechanics: an analytic approach with a viscoelastic model. J Appl Physiol 74: 2373–2379
8. Kano S, Lanteri CJ, Duncan AW, Sly PD (1994) Influence of nonlinearities on estimates of respiratory mechanics using multilinear regression analysis. J Appl Physiol 77: 1185–1197
9. Peslin R, Gallina C, Saunier C, Duvivier C (1994) Fourier analysis versus multiple linear regression to analyse pressure-flow data during artificial ventilation. Eur Respir J 7: 2241–2245
10. Dewachter P, Vassiliou M, Saunier CG, Hartemann D, Peslin R, Laxenaire MC (1997) Effect of the inhibitor of NO synthase, NG-Nitro-L arginine methyl ester, on histamine-induced bronchospasm in the rabbit. Acta Physiol Scand 161: 47–53
11. Nikiscin W, Gerhardt T, Everett R, Bancalari E (1998) A new method to analyse lung compliance when pressure-volume relationship is nonlinear. Am J Respir Crit Care Med 158: 1052–1060
12. Bates JHT, Ludwig MS, Sly PD, Brown K, Martin JG, Fredberg JJ (1988) Interrupter resistance elucidated by alveolar pressure measurement in open-chested normal dogs. J Appl Physiol 65: 408–411
13. Kochi T, Okubo S, Zin WA, Milic-Emili J (1988) Flow and volume dependence of pulmonary mechanics in anesthetized cats. J Appl Physiol 64: 441–450
14. Kochi T, Okubo S, Zin WA, Milic-Emili J (1988) Wall and respiratory system mechanics in cats: effects of flow and volume. J Appl Physiol 64: 2636–2646
15. D'Angelo E, Carderini E, Torri G, Robatto MF, Bono D, Milic-Emili J (1989) Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time. J Appl Physiol 67: 2556–2564
16. Tomalak W, Peslin R, Duvivier C (1998) Variations in airways impedance during respiratory cycle derived from combined measurements of input and transfer impedances. Eur Respir J 6: 1436–41
17. Milic-Emili J, Robatto FM, Bates JHT (1990) Respiratory mechanics in anaesthesia. Br J Anaesth 65: 4–12
18. Tantucci C, Corbeil C, Chasse M, Robatto FM, Nava S, Braidy J, Matar N, Milic-Emili J (1992) Flow and volume dependence of respiratory system flow resistance in patients with adult respiratory distress syndrome. Am Rev Respir Dis 145: 355–360
19. Butler J, Caro CG, Alcala R, DuBois AB (1960) Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. J Clin Invest 43: 584–591
20. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chasse M, Braidy J, MiIic-Emili J (1994) Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 150–1311–1317
21. Vassiliou M, Peslin R, Saunier C, Duvivier C (1996) Expiratory flow limitation during mechanical ventilation detected by the forced oscillation method. Eur Respir J 9: 779–786
22. Pepe PE, Marini JJ (1982) Occult positive end-expiratory pressure in mechanically-ventilated patients with airflow obstruction: the auto-PEEP effect. Am Rev Respir Dis 126: 166–170
23. Milic-Emili J, Gottfried SB, Rossi A (1987) Dynamic hyperinflation: intrinsic PEEP and its ramifications in patients with respiratory failure. In: Vincent JL (ed) Intensive Care Med 192–198
24. Smith TC, Marini JJ (1988) Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 65: 1488–1499
25. Gay PC, Rodarte R, Hubmayr RD (1989) The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 139: 621–626
26. Van den Berg B, Stam H, Bogaard JM (1991) Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 4: 561–567
27. Mead J, Turner JM, Macklem PT, Little JB (1967) Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 22: 95–108
28. Mead J (1980) Expiratory flow limitation: a physiologist point of view. Federation Proc 39: 2771–2775
29. Bates JHT, Peslin R (1993) Acute pulmonary response to intravenous histamine at fixed lung volume in dogs. J Appl Physiol 75: 405–411
30. Lutchen KR, Suki B, Zhang Q, Petak F, Daroczy B, Hantos Z (1994) Airway and tissue mechanics during physiological breathing and bronchoconstriction in dogs. J Appl Physiol 77: 373–385
31. Peslin R, Saunier C, Duvivier C, Marchand M (1995) Analysis of low-frequency lung impedance in rabbits with nonlinear models. J Appl Physiol 79: 771–80
32. Kaditis AG, Venkataraman ST, Zin WA, Motoyama EK (1999) Partitioning of respiratory system resistance in children with respiratory insufficiency. Am J Respir Crit Care Med 159: 389–96
33. Officer TM, Pellegrino R, Brusasco V, Rodarte JR (1998) Measurement of pulmonary resistance and dynamic compliance with airway obstruction. J Appl Physiol 85: 1982–1988